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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 01 March 2001 (01.03.01)	
International application No. PCT/AU00/00873	**Applicant's or agent's file reference** 101525
International filing date (day/month/year) 20 July 2000 (20.07.00)	**Priority date** (day/month/year) 20 July 1999 (20.07.99)
Applicant DIEFENBACH, Russell, John et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

03 January 2001 (03.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

AU0000873

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference 101525	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00873**	International Filing Date *(day/month/year)* 20 July 2000	Priority Date *(day/month/year)* 20 July 1999

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] A61K 35/30, 35/76, 38/17; A61P 25/00, 25/02

Applicant

[THE UNIVERSITY OF SYDNEY et al] Westmead Hospital.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[ ]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
3 January 2001	19 June 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **SHUBHRA CHANDRA** Telephone No. (02) 6283 2264

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00873

I. Basis of the report

1. With regard to the **elements** of the international application:*

- [ ] the international application as originally filed.
- [X] the description, pages **1, 5-14**, as originally filed,
  pages , filed with the demand,
  pages **2-4**, received on **14 June2001** with the letter of **13 June 2001**
- [X] the claims, pages , as originally filed,
  pages , as amended (together with any statement) under Article 19,
  pages , filed with the demand,
  pages **15-17**, received on **14 June 2001** with the letter of **13 June 2001**
- [ ] the drawings, pages , as originally filed,
  pages , filed with the demand,
  pages , received on with the letter of
- [ ] the sequence listing part of the description:
  pages , as originally filed
  pages , filed with the demand
  pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

- [ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- [ ] the language of publication of the international application (under Rule 48.3(b)).
- [ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

- [ ] contained in the international application in written form.
- [ ] filed together with the international application in computer readable form.
- [ ] furnished subsequently to this Authority in written form.
- [ ] furnished subsequently to this Authority in computer readable form.
- [ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- [ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. [ ] The amendments have resulted in the cancellation of:
   - [ ] the description, pages
   - [ ] the claims, Nos.
   - [ ] the drawings, sheets/fig.

5. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-20**	**YES**
	Claims	**NO**
Inventive step (IS)	Claims **1-20**	**YES**
	Claims	**NO**
Industrial applicability (IA)	Claims **1-20**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

Novelty (N) 1-20

Claims 1-20 are novel in the light of Topp, K. S. et al, Neuroscience, Vol. 71(4). Pp1133-144(1996).

The citation does not teach that HSV transport in neurons or other cells such as RPE cells involves a direct interaction (i.e. specific binding) between a motor protein such as Kinensin and a structural tegument protein of HSV. Specifically, the citation does not disclose an agent which prevents binding between a structural tegument protein of the virus and a motor protein in the neuron or cell.

Inventive Step (IS) 1-20

As above.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box I

Rule 67 lists the subject matter which under Article 34(4)(a)(i) an international preliminary examination is not required to be carried out. At item (iv) it specifies methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, as such matter. However the agreement between WIPO and Australia further qualifies this by excepting from exclusion any subject matter which is examined under national grant procedures. Claims 1-11 have nonetheless been considered because the identified subject matter does not contravene Australian law.

all three viral components, nucleocapsid, tegument and glycoproteins was inhibited by nocodazole, indicating their dependence on microtubule-associated transport. Brefeldin A, however, inhibited glycoprotein transport but not nucleocapsids confirming that the two are transported along separate pathways and indicating the close association of HSV glycoproteins with Golgi/intermediate compartment membranes.

The present inventors have now obtained useful evidence for the direct interaction between a viral structural tegument protein and an ubiquitous cellular protein. This new information has been used to develop methods and compositions to alter viral transport and movement in cells.

Disclosure of Invention

In a first aspect, the present invention provides a method of preventing or reducing transport of a neurotropic virus within a neuron or cell, the method comprising providing to said neuron or cell a compound preventing binding between a structural tegument protein of the virus and a motor protein in the neuron or cell such that virus transport in the neuron is prevented or reduced.

In a preferred embodiment, the neurotropic virus is Herpes simplex virus (HSV), varicella-zoster virus, or rabies virus. More preferably, the virus is HSV, the structural tegument protein is US11, and the motor protein is kinesin.

The method according to the invention can be carried out by providing a compound to a neuron or cell capable of preventing binding between a structural tegument protein of a neurotropic virus and a motor protein in a neuron or cell.

In one preferred form, the compound is a motor protein-like molecule which binds the structural tegument protein thereby preventing the normal interaction of the virus with cellular motor protein.

The motor protein-like molecule can be any suitable molecule and would include mimics of the motor protein or a parts of the motor protein to which the structural tegument protein binds.

When the motor protein is kinesin in the case of HSV, the kinesin-like molecule can be any suitable molecule and would include mimics of kinesin or a parts of kinesin to which the structural tegument protein US11 of HSV binds.

In another preferred form, the compound is a structural tegument-like molecule which binds to a motor protein of a neuron or cell thereby preventing the normal interaction between the neuron or cell with the virus. The structural tegument-like molecule can be a mimic of a viral tegument protein or a part of the tegument protein to which a cellular motor protein binds. Preferably, the virus is Herpes simplex virus, the structural tegument protein is US11, motor protein is kinesin and the structural tegument-like molecule is a mimic of US11 or a part of US11 to which the motor protein kinesin binds.

Knowing how these types of viruses move in neurons to infect neurons other cells and ultimately form lesions is an important advance and is useful for the development of antiviral strategies. Usually, during the latent state these viruses do not cause any real problems to an individual. It is during the active phase of the virus where clinical manifestations occur and suffering is caused. Preventing the actual transport of the virus down infected neurons should at least combat or prevent the clinical symptoms of re-infection. Similarly, preventing movement up the neuron may prevent the formation of latent state of the virus in ganglia or at least reduce the incidence of re-occurrence of manifestations of the disease in infected individuals.

In a second aspect, the present invention provides a modified neurotropic virus which has lost or has reduced ability to be transported in neurons, the virus comprising a mutation in a tegument protein such that the mutated tegument protein has abnormal interaction with a cellular motor protein.

In a third aspect, the present invention provides use of a compound to prevent or reduce the interaction between a neurotropic viral tegument protein with a cellular motor protein to prevent or reduce viral transport in a neuron.

In a preferred embodiment of the second and third aspects of the present invention, the neurotropic virus is Herpes simplex virus (HSV), varicella-zoster virus, or rabies virus. More preferably, the virus is HSV, the structural tegument protein is US11, and the motor protein is kinesin.

In a fourth aspect, the present invention provides an antiviral composition comprising a compound capable of preventing

binding between a structural tegument protein of a neurotropic virus and a motor protein in a neuron.

Preferably, the neurotropic virus is selected from the group consisting of Herpes simplex virus, varicella-zoster virus, and rabies virus.

Preferably, the virus is Herpes simplex virus, the structural tegument protein is US11, and the motor protein is kinesin.

In one preferred form, the compound is a motor protein-like molecule which binds to the structural tegument protein of the virus thereby preventing normal interaction of the virus with cellular motor protein of a neuron. Preferably, the motor protein-like molecule comprises a mimic of a cellular motor protein or a part of the motor protein to which a structural tegument protein of a virus binds.

In a further preferred form, the virus is Herpes simplex virus, the motor protein is kinesin and the motor protein-like molecule is a mimic of kinesin or a part of kinesin to which the structural tegument protein US11 of Herpes simplex virus binds.

In another preferred form, the compound is a structural tegument-like molecule which binds to a motor protein of a neuron or cell thereby preventing the normal interaction between the neuron or cell with the virus. The structural tegument-like molecule can be a mimic of a viral tegument protein or a part of the tegument protein to which a cellular motor protein binds. Preferably, the virus is Herpes simplex virus, the structural tegument protein is US11, motor protein is kinesin and the structural tegument-like molecule is a mimic of US11 or a part of US11 to which the motor protein kinesin binds.

The composition can further include additives, diluents, excipients and the like which can be used in clinical and health situations.

This study raises many questions about the mechanisms of tegument formation, location of US11 in the tegument of HSV, the potential role of motor proteins other than kinesin(s) and homologous interactions mediating the transport of other neurotropic viruses. Studies to map minimal binding regions of US11 and uKHC and identification of other cellular factors which facilitate or contribute to the interaction will be useful. Inhibition of this interaction by peptides and/or peptidomimetic analogues could provide a new strategy for antiviral treatment for this and other neurotropic viruses. Incorporation of deletions into specifically attenuated live HSV (or other

CLAIMS:

1. A method of preventing or reducing transport of a neurotropic virus within a neuron or cell, the method comprising providing to said neuron or cell a compound preventing binding between a structural tegument protein of the virus and a motor protein in the neuron or cell such that virus transport in the neuron or cell is prevented or reduced.

2. The method according to claim 1 wherein the neurotropic virus is selected from the group consisting of Herpes simplex virus, varicella-zoster virus, and rabies virus.

3. The method according to claim 2 wherein the virus is Herpes simplex virus, the structural tegument protein is US11, and the motor protein is kinesin.

4. The method according to any one of claims 1 to 3 comprising providing to a neuron or cell a compound capable of altering or preventing interaction between a structural tegument protein of a neurotropic virus and a motor protein in the neuron or cell.

5. The method according to claim 4 wherein the compound is a motor protein-like molecule which binds to a structural tegument protein of the virus thereby preventing the normal interaction of the virus and neuron or cell.

6. The method according to claim 5 wherein the motor protein-like molecule comprises a mimic of a cellular motor protein or a part of the motor protein to which the structural tegument protein binds.

7. The method according to claim 6 wherein the virus is Herpes simplex virus, the motor protein is kinesin and the motor protein-like molecule is a mimic of kinesin or a part of kinesin to which the structural tegument protein US11 of Herpes simplex virus binds.

8. The method according to claim 4 wherein the compound is a structural tegument-like molecule which binds to a motor protein of a neuron or cell thereby preventing the normal interaction between the neuron or cell with the virus.

9. The method according to claim 8 wherein the structural tegument-like molecule comprises a mimic of a viral tegument protein or a part of the tegument protein to which a cellular motor protein binds.

10. The method according to claim 9 wherein the virus is Herpes simplex virus, the structural tegument protein is US11, motor protein is kinesin and the structural tegument-like molecule is a mimic of US11 or a part of US11 to which the motor protein kinesin binds.

11. A method according to any one of claims 1 to 10, wherein the method prevents or reduces transport of a neurotropic virus within a neuron.

12. An antiviral composition comprising a compound capable of preventing binding between a structural tegument protein of a neurotropic virus and a motor protein in a neuron or cell.

13. The antiviral composition according to claim 12 wherein the neurotropic virus is selected from the group consisting of Herpes simplex virus, varicella-zoster virus, and rabies virus.

14. The antiviral composition according to claim 13 wherein the virus is Herpes simplex virus, the structural tegument protein is US11, and the motor protein is kinesin.

15. The antiviral composition according to any one of claims 12 to 14 wherein the compound a motor protein-like molecule which binds to a structural tegument protein of the virus thereby preventing the normal interaction of the virus and neuron or cell.

16. The antiviral composition according to claim 15 wherein the motor protein-like molecule comprises a mimic of a cellular motor protein or a part of the motor protein to which a structural tegument protein of a virus binds.

17. The antiviral composition according to claim 16 wherein the virus is Herpes simplex virus, the motor protein is kinesin and the motor protein-like molecule is a mimic of kinesin or a part of kinesin to which the structural tegument protein US11 of Herpes simplex virus binds.

18. The antiviral composition according to any one of claims 12 to 14 wherein the compound is a structural tegument-like molecule which binds to a motor protein of a neuron thereby preventing the normal interaction between the neuron or cell with the virus.

19. The antiviral composition according to claim 18 wherein the structural tegument-like molecule comprises a mimic of a viral tegument protein or a part of the tegument protein to which a cellular motor protein binds.

20. The antiviral composition according to claim 19 wherein the virus is Herpes simplex virus, the structural tegument protein is US11, motor protein is kinesin and the structural tegument-like molecule is a mimic of US11 or a part of US11 to which the motor protein kinesin binds.

5

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
101525		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/AU00/00873	20 July 2000	20 July 1999

Applicant

WESTMEAD HOSPITAL et al

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readable form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure

   [ ] because this figure better characterizes the invention

   [X] None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00873

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 35/30, 35/76, 38/17; A61P 25/00, 25/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC A61K AND KEYWORDS BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC AS ABOVE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Derwent, Medline, STN International, File CAPLUS. Keywords: neurotropic, herpes simplex virus, rabies, varicella, tegument, motor protein, kinesin, transport, neuron

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J Virology, (Feb. 2000) 74(4) pp 1827-39 Miranda-Saksena, M. et al Anterograde Transport Of Herpes Simplex Virus Type 1 In Cultured, Dissociated Human And Rat Dorsal Root Ganglion Neurons. (see whole document)	1-19
P,X	J Virology, (Oct. 1999) 73(10) pp 8503-11 Holland, D.J. et al Anterograde Transport Of Herpes Simplex Virus Proteins In Axons Of Peripheral Human Fetal Neurons: An Immunoelectron Microscopy Study. (see whole document)	1-19
X	Neuroscience, (Apr. 1996) 71(4) pp 1133-44 Topp, K.S. et al Centripetal Transport Of Herpes Simplex Virus In Human Retinal Pigment Epithelial Cells *in vitro*. (see whole document)	1-19

[X] Further documents are listed in the continuation of Box C - [ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2000	-6 SEP 2000
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **BERNARD NUTT** Telephone No : (02) 6283 2491

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00873

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Proc. Natl. Acad. Sci. U.S.A. (July 2000), 97(14) pp 8146-8150 Bearer, E.L. et al Retrograde Axonal Transport Of Herpes Simplex Virus: Evidence For A Single Mechanism And A Role For Tegument. (see whole document)	1-19
P,X	J Virology, (Feb. 2000) 74(3), pp 1355-1363 Ye, Guo-Jie et al The Herpes Simplex Virus 1 UL34 Protein Interacts With A Cyotplasmic Dynein Intermediate Chain And Targets Nuclear Membrane. (see whole document)	1-19